RADIATION AND AGING*

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My own introduction to awareness of old age was a mixed one. A long and delightful association with a grandfather who took me fishing and told me stories based on his Civil War experiences provided a wonderful counterbalance to my later awareness of the related infirmity and death. This was sharpened by slow and tedious wading through Cicero's *De Senectute*, where the details of translation, parsing, and syntax soon wiped out the rhythmic flow of the Latin and the stilted but pleasantly consoling sentiments wrapped in it.

Through medical school the spotlight was thrown for us on the process of aging; the inexorable death rates for each disease climbed sharply as life advanced: arteriosclerosis, cancer, pneumonia, renal disease. But the steadily advancing programs in public health brought under control the infectious diseases, largely wiped out their mortality, and this led to the steady increase in life-span that has brought our present average age at death to a little over 70 years. As this goal of greater longevity has been brought within our grasp, our attention shifts from the mere span of years lived to concern with the quality of that living.

One of the significant means of keeping death at bay has been man-made radiation with its aids to diagnosis of disease or injury and its useful but rather less conspicuous contribution to therapy. But, as with all good things, whether it be a feast that precipitates coma in the diabetic or the comradely warmth of a fire in the fireplace that kills if the fire becomes a conflagration, radiation in excess is harmful; it may kill immediately and it may cause latent harm that becomes manifest in the future.

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As interest in the cellular effects of radiation grew, it became apparent that one of these was accelerated cellular differentiation.[1] Differentiation as it increases the ultimate specialized role of the cell tends to decrease its ability to proliferate and hence may be regarded as one of the evidences of aging. Among the early suggestions that shortening of life-span by radiation might be associated with precocious aging were those of Russ and Scott,[2] Brues and Sachar,[3] Warren,[4] Upton,[5] and Curtis.[6] Many accepted evidences of aging, such as graying of the hair, loss of hair, development of cataracts, or vascular degeneration, are results produced alike by natural aging and by exposure to ionizing radiation. Almost all types of cells capable of proliferation, normal or neoplastic, suffer arrest of mitosis when irradiated. If they survive, they often tend to become better differentiated and lose their ability to divide to a greater or less degree.

Such observations have led Curtis[7] and others to deduce that the organism as a whole when subjected to ionizing radiation aged much as did many of its component cells.

However, there are dissimilarities as well as resemblances between many effects of radiation and those of aging. Careful study sometimes reveals that quite different mechanisms are involved in the production of similar end results. For example, the early radiation-induced cataract can be clearly differentiated from senile cataract by its location in the lens.[8]

Analysis of many animal experiments shows that we still lack entirely satisfactory criteria for quantitating the nature and extent of the process of aging. Changes in supporting tissues from collagen to bone are recognizable but difficult to quantitate with the passage of time. Most cellular changes are indefinite.

Radiation has been clearly demonstrated to induce a variety of forms of cancer in experimental animals and in man, many of which also increase in frequency with the aging process as they occur spontaneously; epidermoid cancer of the skin and leukemia are prominent examples. In the experimental animal and to some extent in man, there is clear evidence that radiation not only hastens the onset of cancer but increases the actual numbers of cases as well, and does so in a manner roughly proportionate to dose.

Not only does radiation increase the incidence of many lesions associated with advancing age such as cancer, hence shortening life, but it tends to advance in time the appearance of these and other lesions, even those tumors that occur in younger animals such as thymic lymphoma and ovarian tumors.[5] As Blair[9] has pointed out, in the cases of induction of bone tumors in the dog and cutaneous tumors in the rat, the development of tumors may occur in two ways—with high doses the cancer often appears promptly; with lower doses there is a long latent period before it appears.

Experience in man seems to indicate that the induction of a tumor usually requires a long latent period. In the Hiroshima-Nagasaki survivors, where the exposure to radiation was almost instantaneous, the peak period for incidence of leukemia occurred about 10 years after the bombing. In case of the repeated small exposures received occupationally by some radiologists, the leukemia that developed did not appear until after the first 15 years of professional life,[10] perhaps because some time was required to accumulate a leukemogenic dose, perhaps because the mechanism suggested by Blair[9] was operative.

Even with high-dose levels a smaller proportion of an exposed human population appears to develop tumor as compared with animal populations. Thus, with selected strains of mice, incidence levels of leukemia of 75% or more may be obtained, whereas in man the incidence is far less, even in the Japanese survivors closest to the hypocenter of the bombs. Also, Hutchison[11] found no increase in leukemia in an international survey of women cured of cancer of the cervix; portions of their bone marrow had received thousands of rads in the course of treatment. The incidence of cancer of the skin in exposed radiologists is on the basis of exposure to comparable, though estimated, doses, less than that in rodents.

Shortening of life due to other and less specific disease processes than cancer has become recognized as a factor added to the effects of the well-established cancers and leukemia which afflicted a number of the early radiologists, especially those whose enthusiasm for aiding their patients had outrun their understanding of the need to protect themselves. Those who learned early to protect themselves effectively, such as most of the radiologists in the United Kingdom who entered practice after 1921,[12] suffered little damage, but their American colleagues, perhaps because of differences in methods of practice, had shortened lives, as compared with the adult white male population of the United States.[4, 13] As radiologists became more careful and standards of radiation protection were better observed, this shortening of life began to diminish, and by the mid-1960's radiologists had become longer-lived than the adult white male population.[14] Some of this improvement was due to a dip in more recent years[15] in the excess of leukemia among radiologists.

However, factors other than cancer enter the picture. The rates for coronary disease were higher for radiologists (392.6/100,000) than for adult white males in 1950 (349.9/100,000).[14] In addition, Seltser and Sartwell[13] found that the mortality ratios for radiologists for the years 1935 to 1958 were 1.4 times that expected for all cases, and 1.2 times for cardiovascular renal diseases. However, in a study of the Hiroshima-Nagasaki survivors, the data from the Technical Reports for 1969[16] indicate no excess nonspecific mortality. These Japanese findings may be clouded by the existence of the effect of the general disaster on all survivors, those irradiated as well as those not irradiated, caused by the partial starvation, poor shelter, and prevalence of infectious diseases which followed the bombing of the two cities.

While there is not yet clear proof of nonspecific age-shortening in man, its widespread occurrence in animals and some evidence of its occurrence in man suggest that radiation-induced shortening of life may be a general biological phenomenon.

It has been suggested that radiation might shorten life by several mechanisms. The presence of excess numbers of cases of leukemia and other cancers in a limited group—this is known to be true both for many species of experimental animals and for man—would tend to reduce the average age at death of all members of the group. A general effect of radiation might be to add a little to nonspecific mortality throughout subsequent life. Radiation might produce a general loss of vigor so that the degenerative changes characteristic of age would appear earlier, but any specific disease process once induced would then progress at its regular rate. Radiation might speed up the operation of all factors involved in mortality related to age in all exposed; or the process might affect only certain individuals, whereas others showed no shortening of life-span but the combination of the two produced an average shortening of life[17] for the group as a whole.

The interesting observation has been made that the rate of recovery from radiation damage is much decreased in animals that consume a protein-deficient diet.[18] X radiation tends to arrest the progress of cells from one phase to another, so that they remain in phase G2 rather than going into mitosis; if they are in mitosis this period is prolonged. Less harm is done by radiation during protein deficiency but recovery is much slower.[18]

The bulk of observations on animals and man seem to support the hypothesis that there is a general decrease in well-being, which affects those exposed to excessive amounts of ionizing radiation, even though there may have been apparent early recovery from the evidences of radiation damage. If large numbers of animals are studied, most of those irradiated die sooner than the controls. There appear to be no new causes of death induced by radiation; instead, there is a general acceleration of a number of causes. These causes often tend to vary with different species of animals. The suggestion has been made that radiation, a powerful mutagen, may produce mutations in somatic cells that lead to gradual functional deterioration, made manifest by the symptoms of senescence.[7] However, much more information must be gained before the relation of radiation to the aging process can be resolved; indeed, more work must be done before the nonspecific aspect of aging ascribable to radiation is as clearly demonstrable in man as it is in animals. The weight of evidence at present seems to be that this general radiation-caused decrease may often be combined with the induction of specific life-shortening disease processes induced by radiation such as cancer, and that the combination contributes to the shortening of life.

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